REMARKS

Applicant requests reconsideration. Claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68 and 71-76 were previously pending and are still pending and under examination in this application. Claims 1, 21 and 68 has been amended to clarify claim language. No new matter has been added.

Rejections Under 35 U.S.C. §103

Claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75 and 76 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Rodriguez-Moran et al. (1999) in view of Rohfling et al. (2000) and Chapin et al. (1999). The Examiner continues to maintain that"[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made [to] measure serum CRP levels for uses such as characterizing a risk profile for developing diabetes in an apparently healthy individual or evaluating the likelihood that an individual will benefit from treatment given CRP's known association with type II diabetes, as taught by Rodriguez-Moran et al., given that it is well known to measure a known marker for the presence of, or predisposition to, diabetes as taught by Rohfling et al., even in apparently healthy individuals because even apparently healthy individuals can suffer from undiagnosed diabetes and/or complications thereof, as taught by Chapin et al."

Applicant respectfully disagrees and requests reconsideration of the rejection. A person of ordinary skill in the art would not have been motivated to combine the teachings of Rodriguez-Moran et al., Rohfling et al. and Chapin et al. because none of the cited references either alone or in combination provide any teaching that C-reactive protein (CRP) levels can be used to predict the risk of developing *future* diabetes and diabetes complications in subjects before the diabetic disorder develops. To the contrary, the teachings of the references themselves would not have led the skilled artisan to the combination. The combination would only have been effected using hindsight reasoning as discussed below.

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S.___, ____, 82 USPQ2d 1385 (2007) held that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." The key to supporting any rejection under 35 U.S.C.

§103 is the clear articulation of the reason(s) why the claimed invention would have been obvious, and an explicit analysis in supporting such a rejection (emphasis added).

The Examiner has failed to establish a *prima facie* case of obviousness. None of the cited references, alone or in combination, include all of the elements recited in each of Applicant's independent claims. Moreover, the Examiner has also not articulated a rationale nor provided a clear reason why, based on the teachings of the prior art, CRP levels can be used to predict the risk of developing *future* diabetes and diabetes complications in subjects before the diabetes develops.

One of ordinary skill in the art would have recognized that the results of the combination were not predictable. In particular, Rodriguez-Moran et al. does not and could not address the possibility of using CRP levels to predict the risk of developing future diabetes and diabetic complications in apparently healthy individuals who do not have the disease. The goal of the study conducted by Rodriguez-Moran et al. was to identify the relationship between serum CRP and glucose levels in noncontrolled type II diabetic patients (pages 211-212). Rodriguez-Moran compared the serum levels of CRP in hyperglycemic type II diabetic subjects with healthy controls and found that patients with type II diabetes had higher levels of CRP compared to the healthy controls. Furthermore, Rodriguez-Moran et al. suggest that these elevated CRP levels may be the result of the diabetic condition rather than the cause of the diabetes (see Rodriguez-Moran et al. p. 215 right-hand column):

> "A probable involved pathway could be related to the raising of serum viscosity and shear stress associated to hyperglycemia, producing endothelium dysfunction and inflammation and in this way, increasing cytokines release and thus elevating CRP levels."

Based on Rodriguez-Moran et al., the only conclusions that a skilled artisan could make are that in subjects who already have the diabetic disorder, CRP levels are elevated and that these elevated CRP levels are probably a result of the diabetic condition. One of ordinary skill in the art could not make any conclusions regarding the ability of CRP levels to predict the risk of developing *future* diabetes in apparently healthy individuals. In fact, a skilled artisan would have no expectation that CRP levels will be increased in individuals before they develop the diabetic disorder because Rodriguez-Moran et al. suggest that the elevated CRP levels are the result of or are caused by the diabetes. Thus, Rodriguez-Moran et al. teaches away from the idea of using CRP

levels to predict diabetes in apparently healthy individuals who do not have any diabetic disorder, and one of ordinary skill in the art would not have been motivated to use CRP levels to predict the risk of developing *future* diabetes in individuals who do not have the disorder.

The additional teachings of Rohfling et al. and Chapin et al. do not cure the deficiency of the primary reference of Rodriguez-Moran. The Examiner alleges that it is well known to measure a known marker for the presence of, or predisposition to, diabetes and cites Rohfling et al. in support of this.

Applicant respectfully disagrees. Rohfling et al. evaluated the use of GH_b as a screening test for undiagnosed diabetes. In Rohfling et al., subjects with fasting plasma glucose $\geq$7.0 mmol/l were classified as having diabetes, while those with fasting plasma glucose <7.0 mmol/l were classified as not having diabetes. This data was then compared to that obtained using the GH_b screening test in an effort to evaluate the sensitivity and specificity of GH_b for diabetes screening. Thus, the subjects identified in Rohfling et al. had diabetes which was previously undiagnosed. Rohfling et al. do not teach or suggest that CRP levels or the GH_b screening test can be used to determine the predisposition of a subject to develop *future* diabetes.

Similarly, the objective of Chapin et al. was to evaluate the presence of undiagnosed diabetes among US Army soldiers, and not the predisposition to develop *future* diabetes. The subjects identified by Chapin et al. had diabetes which remained undetected until the study was conducted.

Thus, the subjects of both Rohfling et al. and Chapin et al. cannot be considered as "apparently healthy" as described in the instant specification. Apparently healthy individuals as defined in the instant specification on page 9, lines 4-7 do not exhibit symptoms of diabetes, and if examined by a medical profession would be characterized as healthy and free of symptoms of the disease. By contrast, on evaluation the subjects in both Rohfling et al. and Chapin et al. were found to have diabetes as their blood glucose concentration satisfied the ADA and/or the WHO criterion. As a result, these subjects would not be classified as healthy and free of the disease (i.e., they are not apparently healthy).

The instant application is based on the discovery that elevated levels of certain markers of systemic inflammation are predictive of *future* development of diabetes or diabetic complications.

In particular, individuals with highest baseline levels of CRP were found to have more than a 10-fold increase in risk of developing *future* diabetes.

The Examiner has continued to assert that although Rodriguez-Moran et al. did not address whether CRP levels could predict future diabetes, "the skilled artisan would have combined the teachings of all of the references to develop a method for predicting future diabetes as set forth above."

Applicant respectfully disagrees. The data presented in the application greatly extend prior observations which have suggested that CRP levels are increased among individuals who already are known to have the diabetic disorder. Prior to the instant application, it was uncertain whether statistical associations observed in former studies of individuals with known diabetes are causal or due to short term inflammatory changes, or to interrelations with other risk factors, in particular obesity and hyperlipidemia. In the absence of such teachings, one of ordinary skill in the art would have no expectation of success and hence, would not be motivated to combine the cited references as asserted by the Examiner.

According to the Examiner, the majority of the cases in the instant study did not meet Applicant's definition of "apparently healthy".

Applicant respectfully disagrees. The case subjects who participated in the trial described in the specification were free of reported diabetes at enrollment. Due to the high prevalence of undiagnosed diabetes among middle-aged Americans and because the study was designed to evaluate the role of inflammation as a determinant of *future* diabetes, the inventors restricted their case subjects to individuals with baseline hemoglobin A1c <6.5%, which is a reference commonly used in clinical practice. In addition, to reduce misclassification bias due to undiagnosed diabetes at study entry, individuals diagnosed with diabetes within the first year of follow-up were excluded from the study. Moreover, CRP remained a significant predictor after adjusting for body mass index, hypertension, family history of diabetes, exercise frequency, alcohol consumption, hyperlipidemia, smoking and menopausal status. Thus, elevated levels of CRP in healthy individuals are predictive of an increased risk of a diabetes or diabetic complications even after controlling for other factors such as obesity, hypertension, hyperlipidemia, and a family history of diabetes. Thus, contrary to the allegations made in the Office Action, the case subjects used in the

instant study were free of reported diabetes at the time of enrollment, and every effort was made to reduce misclassification bias due to undiagnosed diabetes and to adjust for a large series of other risk factors.

None of the cited references teach or suggest that CRP levels can be used to predict the risk of developing *future* diabetes. The skilled artisan would not have combined the cited references in the manner suggested by the Examiner since it was suggested in Rodriguez-Moran et al. that the elevated CRP levels are the result of or are caused by the diabetes. The choice of a specific level of serum CRP concentration as a significant predictor of the risk of developing future diabetes is taught only in the instant specification.

Applicant respectfully submits that the Examiner's combination of the prior art elements stem from an improper application of hindsight reasoning based on the teachings of the present application. Applicant notes that "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." In re Wesslau, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965); see also In re Mercer, 515 F.2d 1161, 1165-66, 185 USPQ 774, 778 (CCPA 1975); In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987).

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a).

Claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75 and 76 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schalkwijk et al. (1999) in view of Rohfling et al. (2000) and Chapin et al. (1999). The Examiner states that "Schalkwijk et al. does not teach the characterizing a risk profile for developing diabetes in an apparently healthy individual" and that "[i]t would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to measure serum CRP levels for uses such as characterizing a risk profile for developing diabetes in an apparently healthy individual, as taught by Schalkwijk et al."

Applicant respectfully disagrees. Similar to Rodriguez-Moran et al., Schalkwijk et al. did not evaluate individuals who were apparently healthy (i.e., without diabetes). Instead, CRP

concentrations were measured in patients with Type I diabetes mellitus. Schalkwijk et al. found that the median plasma concentration of CRP was higher in Type I diabetic patients compared to healthy controls. Furthermore, Schalkwijk et al. suggest that these elevated CRP levels may be the result of the diabetic condition rather than the cause of the diabetes (see Schalkwijk et al. p. 356):

> "Various possible mechanisms could induce chronic low degree inflammation in diabetes, including activation of macrophages, increased oxidative stress or an induction of cytokines. One of the pathophysiological consequences of hyperglycaemia is the phenomenon of nonenzymatic glycation and the formation of advanced glycation end products (AGEs). AGEs have been shown to activate macrophages, to increase oxidative stress and to induce, in macrophages, the synthesis of interleukin-1 and tumor necrosis factor-α and, in vivo in mice, the expression of interleukin-6 mRNA. Many of the possible mechanisms leading to chronic low degree inflammation could be related to nonenzymatic glycation. Another possibility is that increases in CRP are related to adipose-tissue-derived cytokines." (Citations omitted)

Based on Schalkwijk et al., the only conclusions that a skilled artisan could make are that in subjects who already have the diabetic disorder CRP levels are elevated, and that these elevated CRP levels are probably a result of the diabetic condition.

The Examiner states that "[r]egarding whether or not elevated CRP is the cause of, or the result of diabetes is irrelevant."

Applicant respectfully disagrees and asserts that a skilled artisan would have no expectation that CRP levels will be increased in individuals before they develop the diabetic disorder since the cited prior art suggest that the elevated CRP levels are the result of or are caused by the diabetes. Thus, similar to Rodriguez-Moran et al., Schalkwijk et al. teaches away from the idea of using CRP levels to predict diabetes in apparently healthy individuals who do not have any diabetic disorder, and one of ordinary skill in the art would not have been motivated to use CRP levels to predict the risk of developing *future* diabetes in individuals who do not have the disorder.

Accordingly, the teachings of Schalkwijk do not render the claimed methods obvious and withdrawal of the rejection is respectfully requested.

Claims 11, 16, 73 and 74 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Rodriguez-Moran et al. (1999) in view of Rohfling et al. (2000) and Chapin et al. (1999) as

applied to claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75 and 76, and further in view of Dods and Bolmey et al. (1979). Further, claims 11, 16, 73 and 74 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Schalkwijk et al. (1999) in view of Rohfling et al. (2000) and Chapin et al. (1999) as applied to claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75 and 76, and further in view of Dods and Bolmey et al. (1979).

The Examiner asserts that "[g]iven the teachings of Dods and Bolmey it would have been obvious to employ the method of Dods and Bolmey in combination with the combined method of Rodriguez-Moran et al., Rohfling et al., and Chapin et al. to achieve a superior or more accurate prediction of diabetes given that an assay for HbA is more routine in the screening for diabetes and that multiple methods of screening are often combined to establish the presence of disease." (page 6 of the Office Action).

Applicant respectfully traverses the rejection. The teachings of Rodriguez-Moran et al., Schalkwijk et al., Rohfling et al., and Chapin et al. have been discussed above and are applicable here but are not repeated here. Dods and Bolmey compared the oral glucose tolerance test (evaluated by six commonly used scoring methods) to the total glycohemoglobin assay, and found that depending of the evaluation method used for the oral glucose tolerance test, 16.7 to 64.3% of the subjects diagnosed as diabetic or borderline by this test were judged to be normal by the total glycohemoglobin assay. Dods and Bolmey did not evaluate individuals who were apparently healthy (i.e., without diabetes). Instead, 27 patients hospitalized for uncontrolled diabetes mellitus were assayed using the oral glucose tolerance test and the total glycohemoglobin assay. Based on this study, one of ordinary skill in the art could not make any conclusions or predictions regarding the ability of the total glycohemoglobin assay to predict the risk of developing future diabetes in apparently healthy individuals. Moreover, in view of the poor correlation between the two tests, one of ordinary skill in the art would not conclude that diabetes is generally diagnosed using multiple screening methods.

The instant application is based on the discovery that the predictive value of certain markers of systemic inflammation are independent of other predictors and are least additive with risk factors such as glycosylated hemoglobin screening. Thus, the level of markers of systemic inflammation does not simply duplicate that which is measured when levels of a second risk factor (e.g.,

glycosylated hemoglobin) are obtained. Thus, the combination of these two methods of early detection is substantially better than that associated with current methods.

In view of the above arguments, withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §102

Claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75, and 76 have been rejected under 35 U.S.C. §102(b) as being anticipated by Ford (1999).

For anticipation, each and every element set forth in the claim must be found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP 2131. The cited reference does not anticipate the pending claims because the cited reference does not teach each and every element of the claimed invention. The instant claims are directed to methods for characterizing an apparently healthy individual's risk profile of developing future diabetes or a diabetic complication comprising obtaining a level of CRP in a blood sample from an individual and characterizing the individual as having an increased risk of developing future diabetes or a diabetic complication if the level of CRP is about 0.30 mg/dl or higher.

Ford examined the relationship between CRP and BMI and diabetic status and found that CRP levels were elevated in individuals with newly or previously diagnosed diabetes. Ford did not address the possibility of using CRP levels to predict the risk of developing *future* diabetes and diabetic complications in apparently healthy individuals who do not have the disease. Ford does not teach that a specific CRP serum concentration (about 0.30 mg/dl) can be used as a significant predictor of future diabetes in apparently healthy individuals. Ford does not provide a teaching that apparently healthy individuals can be characterized as having an increased risk of developing future diabetes based on their blood CRP levels. Instead, all that the cited reference teaches is that CRP levels are elevated in individuals with diabetes.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §112

Claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68 and 71-76 have been rejected under 35 U.S.C § 112, second paragraph, as being indefinite. According to the Examiner, "it is unclear whether or not the "characterizing" and "comparing" of the claims are actually steps, or not, and further, precisely what the "characterizing" encompasses. The Examiner alleges that "characterizing" is not defined in the specification, the metes and bounds of the actual action of the step cannot be determined.

Without conceding the correctness of the rejection and in the interest of expediting prosecution, Applicant has amended claims 1, 21 and 68.

Applicant respectfully disagrees with the Examiner's assertion that it is "unclear" what the term "characterizing" encompasses. The term "characterizing" is recognized and discernable to one of ordinary skill and allows the reader to apprise the scope of the claim as a whole. A claim term that is not used or defined in the specification is not indefinite if the meaning of the claim term is discernible. *Bancorp Services, L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372, 69 USPQ2d 1996, 1999-2000 (Fed. Cir. 2004). Furthermore, the claim as a whole apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. **112**, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time.

If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: September 21, 2009

Respectfully submitted,

By _____

Roque El-Hayek
Registration No.: 55,151
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000